

Influence of Aqueous Extract the Pomegranate Peel on Healing of Gastric Ulcer in Experimental Rats

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ABSTRACT: In the present study the antiulcerogenic effects of aqueous extract of Pomegranate Peel (PP), was tested on male Sprague Dawley rats. Oral treatment with PP (200, 400 and 600 mg/kg) for 21 days protected the gastric mucosa against the damage induced by aspirin (200mg/kg). Anti-ulcer activity of PP was evaluated by measuring the Ulcer Index (UI), Volume of Gastric Juice (VGJ), PH of the gastric fluid and histopathologic changes. The best results were found in a dosage of 600 mg/kg of PP, which showed significant inhibition of UI (1.32 ± 0.05) and VGJ (2.3 ± 0.01 ml), as well as showed significant increase of pH (4.09 ± 0.07) in comparison with aspirin induced gastric ulcer group. Also the high dose of pp markedly reduced the severity of inflammatory reactions in lamina propria and muscularis in fore and glandular stomach. From the preliminary finding of our study it was concluded that the PP has a significant ulcer healing property. Further investigations are needed to fully understand the mode of action of the active constituents and to fully exploit pomegranate's preventive and therapeutic potential.

Keywords: Aspirin; Pomegranate peel; Peptic Ulcer; Rats.

1-INTRODUCTION

The prevention or cure of gastric ulcers is one of the most important challenges facing medicine nowadays. In addition, gastric ulcer therapy faces multiple drawbacks including: the currently marketed drugs revealed limited efficacy and associated with severe side effects (Mota et al., 2009). Gastric ulcer occurs mainly due to the imbalance between the destructive and protective factors to the mucosal barrier. The destructive factors include stomach Hydrochloric Acid (HCl), free oxygen radicals, ethanol, Helicobacter pylori and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) that encourage the gastric mucosal injury leading to of ulceration (Al-Wajeih et al., 2017).

Aspirin is acetylsalicylic acid often used to treat pain, fever and inflammation (Derry et al., 2012). Despite its therapeutics benefits, it was known to induce gastric ulcer in both human and animals (Sørensen et al., 2012). Studies have demonstrated that the use of aspirin is associated with side effects, especially peptic ulcerations and gastrointestinal bleeding (Shikawa et al., 2008). The pathogenesis of aspirin-induced gastric ulceration includes the aspirin blocking the activities of the cyclooxygenase enzymes (COX-1 and COX- 2) hence leading to reduced mucus and bicarbonate secretion, decreased mucosal blood flow, impaired platelet aggregation, alteration of microvascular structures leading to epithelia damage, increased leukocyte adherence and increased production of reactive

oxygen species (ROS), increased lipid peroxidation and neutrophil infiltration as well as decreased antioxidant enzymes (Adefisayoa et al., 2017).

Punica granatum L. (Punicaceae), commonly called pomegranate, recently described as nature's power fruit, widely cultivated in the Mediterranean region (Abdel Moneim, 2011). It is widely consumed, fresh and in commercial products, such as juices and jams, as well as their products are commonly used in the cure of diseases since ancient time (Panichayupakaranant et al., 2010). Such ingredients of Pomegranate has therapeutic role, peels of the pomegranate covers around 60% of the fruit and they hold various types of ingredients including flavonoids, ellagitannins and proanthocyanidin compounds and minerals such as calcium, magnesium, phosphorus, potassium and sodium (Mirdehghan & Rahemi, 2007).

Moghaddam et al. (2014) indicated that the most extracts of pomegranate peel had both anti-inflammatory and anti-ulcerogenic. Furthermore, Bachoual et al. (2011) found that *Punica granatum* peel aqueous extract (PGE) is widely used to treat disorders such as inflammation, ulcers and infections, but its pharmacological target is not known. Meanwhile, katary and salahuddin (2017) have been indicated that antioxidant and antiulcer activity of *Punica granatum* may be due to the presence of phenolic punicalagins; gallic acid and other fatty acids; catechin, quercetin, rutin; flavones, flavonones; anthocyanidins, which could produce significant gastroprotective effects via suppression of mucosal oxidative stress and inflammation as well as replenishing of nitric oxide and mucin content. Also they suggested that punicalagin could have a protective effect for additional progress as a promising drug for ulcer treatment.

Gastric ulcer therapy faces a major drawback due to the unpredictable side effects of the long term use of commercially available drugs (Cadirci et al., 2007). Hence, the research are still on to find drug possessing antiulcer properties, which will serve as a powerful therapeutic agent to cure gastric ulceration, and the research extend to the systematic development of natural products (Zhang et al., 2012). Therefore, the development of safe anti-ulcer of natural origin is a target in modern nutritional research. The objective of the present study is to investigate the possible effect of healing of aqueous extract of pomegranate peel against aspirin -induced gastric ulcer in rats.

2. MATERIALS AND METHODS

2.1- Materials and rats

2.1.1 Aspirin: Aspegic (Mmiriya Pharmaceutical Industries, Cairo) injection was prepared by dissolving one vial in 25ml distilled water to obtain solution. A volume of 1ml of this solution was orally given (at the level 200mg/kg body weight) for one day to induce acute gastric ulcer in male albino rats.

2.1.2 Plants: Pomegranate Peel (PP) (botanical name *Punica granatum*, is a fruit-bearing deciduous shrub or small tree in the family Lythraceae), this plant was purchased from local market of Minufiya, Egypt.

2.1.3 Diet: The rats were fed on ration (a basal diet devoid from starch) composed of wheat bran, soya bean powder 44%, fish meal, molasses, fibers 3.3%, sodium chloride,

calcium carbonate, calcium phosphate, methionine and ash (net protein 22% and fats 4.7%). The diet was fed and water was provided ad libitum for the experimental period.

2.1.4 Rats: Thirty adult male albino rats mean (\pm SD) body weight was 180 (\pm 5) grams of Sprague Dawley Strain were obtained from animal house of the faculty of medicine, Minufiya University, Minufiya, Egypt.

2.2-Methods

2.2.1 Preparation of aqueous extracts:

The clean PP was ground using porcelain grinder to pass through sieve-mesh pores of 1mm diameter. The extract of PP was prepared by mixing 1gm powdered PP with 100 ml distilled water. The mixture was boiled for 10 minutes and left to cool for 15 minutes. The aqueous extract was filtered using filter paper to remove the particulate matter (0.2mm) then the filtrate was freely dried (Lyophilized) and reconstituted in 1.5 ml of distilled water (100 mg/kg body weight).

2.2.2 Grouping design and feeding of rats:

The experiment was performed in animal house of the faculty of medicine, Minufiya University. Rats were housed in wire cages in a room maintained at $25\pm 2^{\circ}\text{C}$ and kept under normal healthy conditions for two weeks. All rats were fed for one week on basal diet before starting the experiment for acclimatization. After one week period, rats were divided into two main groups. The first group (n= 6 rats) was fed on the basal diet only as a control negative (healthy rats). Group 1: Control negative -ve group was fed on ration (non-treated rats). All rats in the second main group (n= 24 rats) were given orally aspirin at a dose of 200mg/kg body weight, for induction of acute gastric ulcer according to Agrawal et al. (2000). Rats with (aspirin-induced gastric ulcer) were disparted into four groups (n= 6rats for each group) as the followings:

Group (2): Control positive group C^+ is given orally aspirin at a dose of 200mg/kg and will be fed on basal ration

Group (3): C^+ rats will be fed on basal ration + aqueous extract of PP at doses of 200 mg/kg B.Wt.

Group (4): C^+ rats will be fed on basal ration + aqueous extract of PP at doses of 400 mg/kg B.Wt.

Group (5): C^+ rats will be fed on basal ration + aqueous extract PP at doses of 600 mg/kg B.Wt.

The experimental period was 21days, the rats remained without food for one day prior to ether anesthesia (except for water) to avoid mixing of food with gastric secretions.

2.2.3 Isolation of stomach and collection of gastric juice:

At the last day of experimental period, all rats were fasted and only water was allowed for 12-14hrs. In the morning of the next day, all rats were sacrificed, and their stomachs were tied around both openings (cardiac & pyloric sphincters). With small nick, fundus of stomach was perforated on greater curvature of stomach. The greater curvature of stomach was opened. The accumulated gastric secretion fluid was collected into graduated microcentrifuge tubes, and volume (in ml) and pH was measured (Patil et al., 2012). Gastric juice was centrifuged at 2000 rpm for 10 min. From the supernatant, aliquots of 1 ml gastric juice were diluted with 1 ml distilled water and pH of the solution was measured

using pH meter (waterproof pocket-sized pH meter, S2K712; Toyorika, Tokyo, Japan) (Gupta et al., 2012). The cleaned stomachs were preserved in 0.1 M phosphatesaline buffer (1:4 (w/v), pH 7.4) prior to macroscopic examination (Akhtar and Ahmad, 1995).

2.2.4 Morphological examination and determination of Ulcer Index and Percentage Healing:

After washing, each stomach was placed on a flat plate to visualize the morphological changes induced by different treatments. Photographs were taken using digital camera with zooming (10 mega pixel 5× zoom). Then, the number of ulcers per stomach was quantified. Ulcers were scored as described by Kulkarni (2002), as 0 for normal colored stomach, 0.5 for red coloration, 1 for spot ulcer, 1.5 for hemorrhagic streaks, 2 for ulcer between (3–5) mm and 3 for ulcer >5 mm. Gastric mucosal injury was assessed by volume of gastric secretion (in ml), pH of gastric secretion and ulcer index (UI). Mean ulcer score for each animal was expressed as ulcer index (UI). The ulcer index was determined as follows: (Gupta et al., 2012)

$$UI = (UN + US + UP) \times 10^{-1}$$

Where: UI = Ulcer Index

UN = Average of number of ulcer per animal

US = Average of severity score

UP = Percentage of animal with ulcer

Percentage healing was calculated by using the formula (Kazmi, et al., 2018):-

$$\% \text{ Healing} = 100 - [Ut / Uc \times 100]$$

Where, Ut = Treated group ulcer index. Uc = Control +ve group ulcer index

2.2.5 Histopathological method:

Specimens from stomachs were collected from rats of all experimental groups at the end of the experimental period, fixed in 10% neutral buffered formalin (pH=7.0), dehydrated in ethyl alcohol, then cleared in xylol and embedded in paraffin; 4-6 microns thickness sections prepared and stained with hematoxylin and eosin for examining both fore and glandular parts of the stomach. Cut sections were observed by the microscope for changes in histo-pathology like hemorrhage, inflammation, tissue damage, erosion, infiltration and ulceration congestion and photographs were taken (Bancroft and Gamble, 2008).

2.2.6 Statistical analysis:

Statistical packaging spreadsheet software Version 20 was used for statistical analysis. Mean ±SE (range), a paired-sample t-test was used to compare the parameters between controls positive group and other rats groups. Value of P lesser than five (P<0.05) was considered to be statistically significant.

3. RESULTS

Pomegranate Peel (PP) was evaluated for anti-ulcer activity, Effect of PP on Ulcer Index and percentage of healing is shown in Table (1) and Fig. (2). The aqueous extract of PP with the doses 200, 400 and 600 mg/kg have produced a significant increase (P<0.05) in

ulcer index of 3.47 ± 0.74 , 2.07 ± 0.25 and 1.32 ± 0.05 , respectively in comparison to control +ve (7.58 ± 0.13). Of these, treatment with PP extract significantly suppressed ($P < 0.05$) the formation of ulcers with increasing doses 200, 400 and 600 mg/kg with significant increase ($P < 0.05$) in healing percentage of 54.29, 72.75 and 82.64, respectively.

Table 1: Effect of pomegranate peel (PP) on ulcer index.

Parameters Groups	Ulcer Index	Healing%	t-test	Sig
Control -ve	0.0 ± 0.0	100	-59.438-	0.000
Control +ve	7.58 ± 0.13			
PP 200 mg/kg	3.47 ± 0.74	54.29	-5.322-	0.003
PP 400 mg/kg	2.07 ± 0.25	72.75	-15.363-	0.000
PP 600 mg/kg	1.32 ± 0.05	82.64	-39.031-	0.000

Values are expressed as (Mean \pm SEM) of 6 rat / treatment.

t-test: Significant difference between Control +ve and other groups.

Significant $P < 0.05$ when compared with +ve Control.

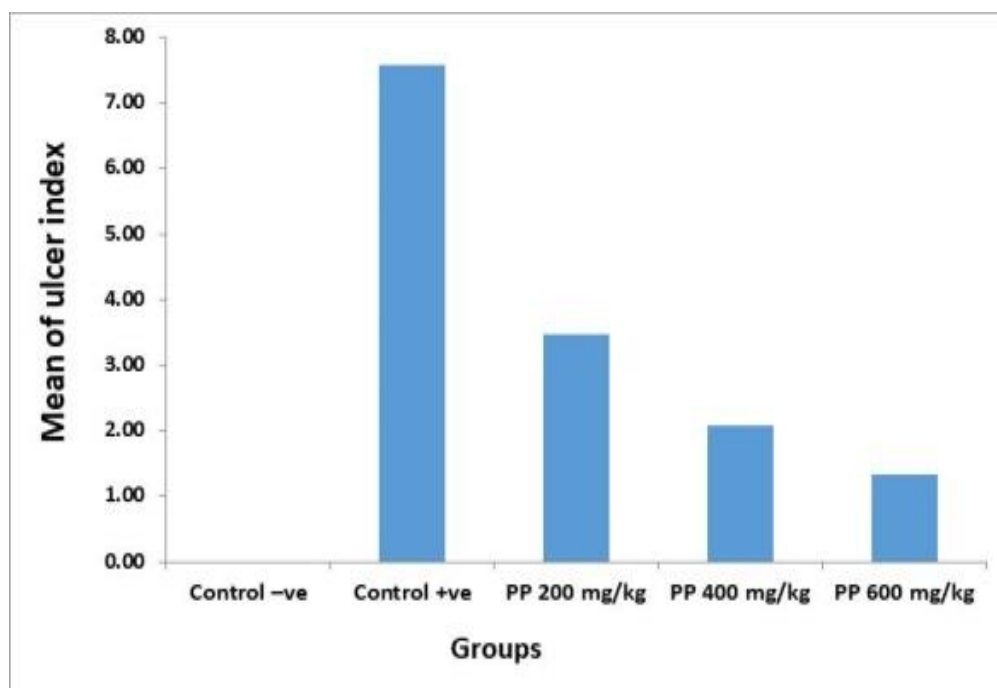


Fig. 1: Effect of PP on UI

Inflammation of gastric mucosal was assessed by increasing gastric secretion, administration of PP in three different doses (200, 400 and 600 mg/kg) showed significant

reduction ($P < 0.05$) in VGJ (4.2 ± 0.04 , 3.1 ± 0.03 and 2.3 ± 0.01 ml, respectively in comparison to control +ve group (7.3 ± 0.04). However, highest dose of PP has shown a highly significant inhibition ($P < 0.05$) in VGJ by 68.51% compared to the control +ve (Table 2 and Fig. 2).

Table 2: Effect of PP on volume of gastric juice (ml)

Parameters Groups	Volume of gastric juice (ml)	inhibition%	t-test	Sig
Control -ve	2.0 ± 0.01	71.96	-13.962-	0.000
Control +ve	7.3 ± 0.04	0.00		
PP 200 mg/kg	4.2 ± 0.04	42.76	-4.577-	0.006
PP 400 mg/kg	3.1 ± 0.03	59.08	-7.110-	0.001
PP 600 mg/kg	2.3 ± 0.01	68.51	-14.431-	0.000

Values are expressed as (Mean \pm SEM) of 6 rat / treatment.

t-test: Significant difference between Control +ve and other groups.

Significant $P < 0.05$ when compared with +ve Control.

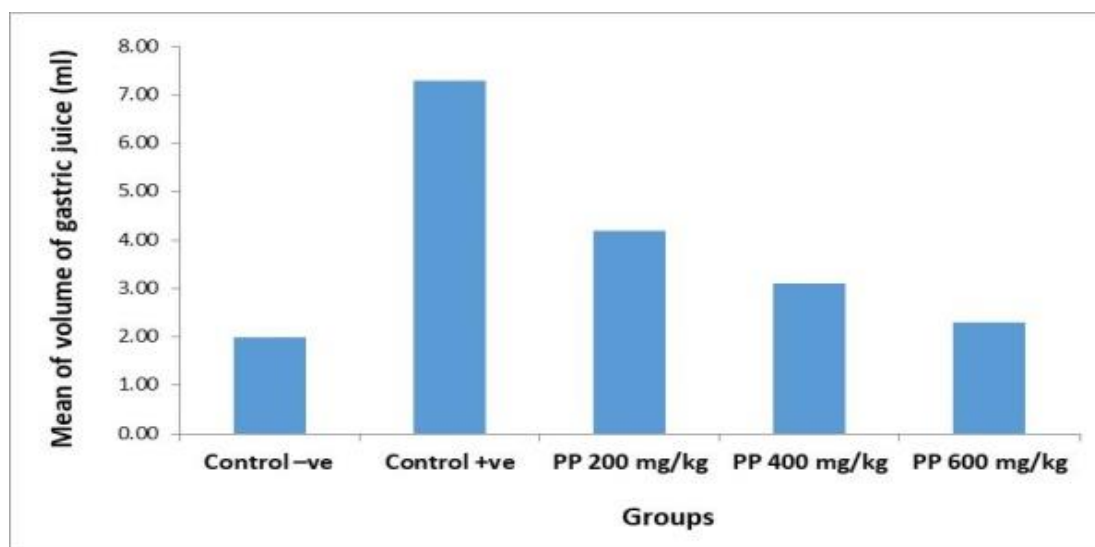


Fig. 2: Effect of PP on VGJ

Gastric mucosal injury was assessed by reduced pH of gastric secretion. As shown in Table (3) and Fig. (3), PP treatment with the doses 200, 400 and 600 mg/kg significantly increases ($P < 0.05$) pH level by 3.48 ± 0.13 , 3.68 ± 0.13 and 4.09 ± 0.07 , respectively as compared to the corresponding control +ve group (2.72 ± 0.15). Furthermore, PP treatment with the dose 600 mg/kg induced a highly significant increase ($P < 0.05$) in stomach secretion pH level by %50.37 compared to the control +ve.

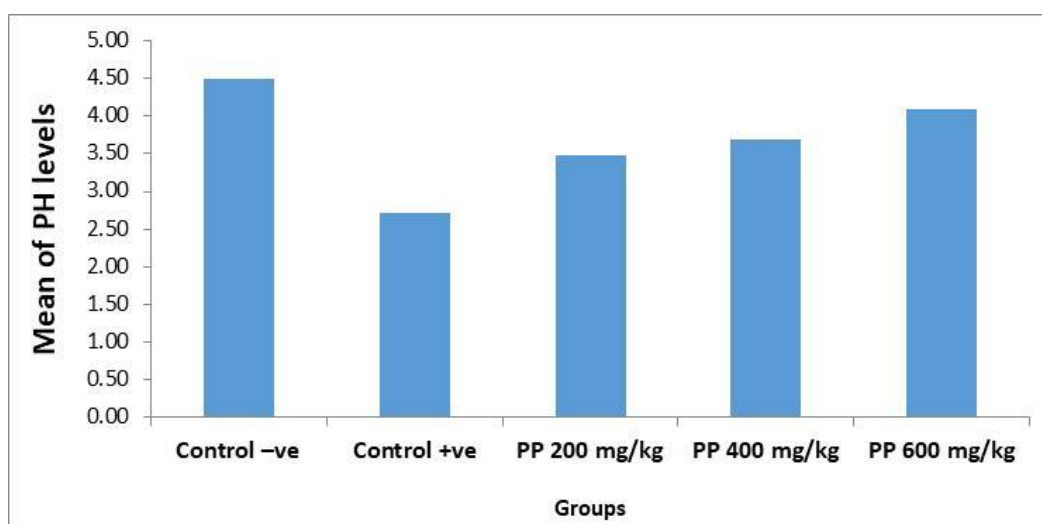
Table 3: Effect of PP on pH.

Parameters Groups	pH	Increase Ratio (%)	t-test	Sig
Control -ve	4.50±0.11	65.44	11.445	0.000
Control +ve	2.72±0.15	0.00		
PP 200 mg/kg	3.48±0.13	27.94	4.858	0.005
PP 400 mg/kg	3.68±0.13	35.29	3.648	0.015
PP 600 mg/kg	4.09±0.07	50.37	10.063	0.000

Values are expressed as (Mean ± SEM) of 6 rat / treatment.

t-test: Significant difference between Control +ve and other groups.

Significant P<0.05 when compared with +ve Control.

**Fig. 3: Effect of PP on PH.**

Histopathological examination of fore and glandular parts of rats stomachs:

Oral administration of a single dose (200 mg/Kg) of Aspirin to rats caused, edema in lamina propria with mononuclear cells infiltration of the stomach (Fig. 5) compared to the normal histological structure in the control-ve group as illustrated in Fig. (4). Stomachs of rat given pomegranate peel at doses of 200 mg/kg B.Wt for 21 days following Aspirin administration slightly decreased the inflammatory cell reaction in lamina propria and muscularis mucosa of glandular stomach as shown in Fig. (6). The dose of pomegranate peel at doses of 400 mg/kg B.Wt., following Aspirin administration produced few inflammatory cells infiltration and edema in lamina propria in the base of the lamina propria in the glandular stomach as shown in Fig. (7). The high dose of pomegranate peel at doses of 600 mg/kg B.Wt markedly reduced the severity of inflammatory reactions in

lamina propria and muscularis in fore and glandular stomach. There was few and focal inflammatory cell infiltrations in glandular stomach as shown in Fig. (8).

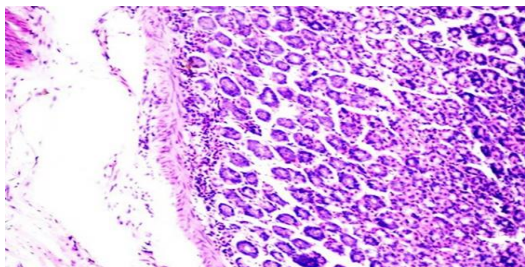


Fig. 4:Normal histological structure in the control –ve group .

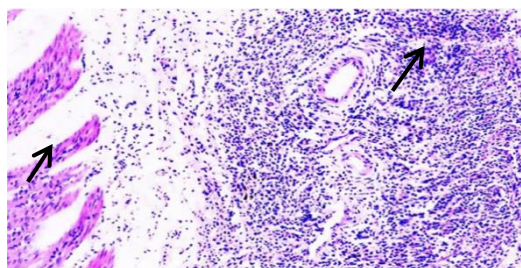


Fig. 5: Oral administration of a single dose (200mg/kg) of aspirin to rats caused edema with massive number of inflammatory cells infiltration in the lamina propria of the mucosal layer in fore stomach also destruction of the mucosal epithelium.

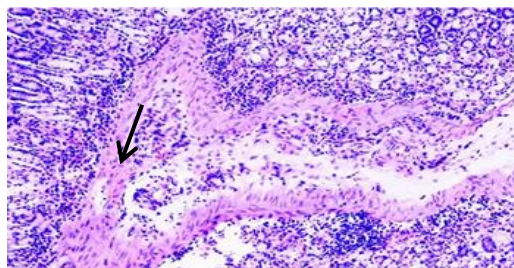


Fig. 6: Rats given pomegranate peel at doses of 200 mg/kg B.Wt for 7 days following aspirin administration slightly decreased the inflammatory cell reaction in lamina propria and muscularis mucosa of glandular stomach.

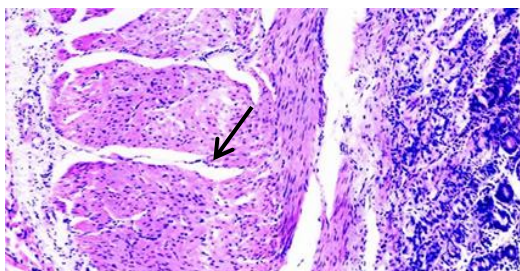


Fig. 7: The dose of pomegranate peel at doses of 400 mg/kg B.Wt. produced few inflammatory cells infiltration in the base of the lamina propria in the glandular stomach .

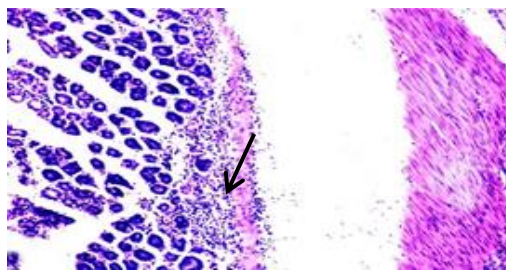


Fig. 8: The high dose of pomegranate peel at doses of 600 mg/kg B.Wt markedly reduced the severity of inflammatory reactions in lamina propria and muscularis in fore and glandular stomach. There was few and focal inflammatory cell infiltrations in glandular stomach.

4- DISCUSSION

Nowadays gastric ulcer is one of the most important concerns as a result of many factors especially wide spread using of nonsteroidal anti-inflammatory drugs (NSAIDs) (Moghaddam et al., 2013). Consequently, it is necessary to develop more effective agents that are also less toxic. The objective of the present study was to study aqueous extract of PP that was evaluated for its anti-ulcer activity against Aspirin induced ulcer model in rats. Based on the present study Aspirin (200 mg/kg) have shown severe ulceration as indicated by ulcer index, volume of gastric acid juice and pH level. Lavie et al. (2017) interpreted the adverse effects of Aspirin and other NSAIDs on the upper gastrointestinal (GI) tract mucosa that might be mediated by both direct and indirect mechanisms. Direct injury results from trapping of high concentrations of Aspirin within gastric epithelial cells. The indirect effects of Aspirin are mediated primarily via inhibition of cyclooxygenase and the resulting reduction in prostaglandin synthesis. This leads to reduction in the secretion of bicarbonate and epithelial mucus, mucosal blood flow, and mucosal proliferation necessary for repair. Consequently, the gastric mucosa becomes more susceptible to injury by exogenous and endogenous substances (e.g. stomach acid and Pepsin) and shows an impaired ability to repair itself (Wallace, 2008). Moreover, the inhibition of platelet aggregation that forms the basis of Aspirin's antithrombotic action will predispose to gastrointestinal GI bleeding once mucosal injury has occurred (Fanaroff and Roe, 2016). From a clinical standpoint, the spectrum of aspirin-induced GI toxicity induced by these mechanisms includes superficial mucosal injury (subepithelial hemorrhage and erosions) and mucosal ulceration; however, this may-then-lead to either hemorrhage or perforation or both, which could lead to death (Wolfe et al., 1999).

Ulcer healing activity of PP in this study is justified by significantly reduced ulceration area and the volume of gastric acid juice and elevated the pH level, the highest tested dose (600 mg/kg) is the most efficient. Similar results were achieved by previous authors (Shekha et al., 2017; Hussein et al., 2014, and Moghaddam et al., 2013) indicating a high antiulcer activity of Pomegranate. Pomegranate induced an increase in mucus production, which was most demonstrative in ulcerogenic rats. Mucus serves as the first line of the defense against ulcerogenic (Hussein et al., 2014). Furthermore, Gautam (2012) reported that, the administration of aqueous peel extract of the pomegranate, show considerable recovery in ulcer as compared to rind and seed of this fruit in Aspirin induced ulcer in rats .The ulcer protective effects of pp may be due to its actions on gastric mucosal defensive factors like an increase in dissolved mucus and decrease in mucosal cell exfoliation (Dorababu et al., 2004). Antiulcer of PP was also attributed to rich pomegranate in ellagic acid, ellagitannins (including punicalagins) (Shukla et al., 2008), alkaloids, such as pelletierine, pseudopelletierine (Kirtikar and Basu, 2000) and punicic acid, flavonoids, anthocyanidins, anthocyanins, and estrogenic flavonols and flavones (Jurenka, 2008).

Pomegranates are a highly valued, functional food that has antioxidant and anti-inflammatory activities in vivo and in vitro (Kim et al., 2017). Ellagic acid, a phenolic lactone compound, is the main in vivo hydrolysis product of pomegranate polyphenols, and possesses anti-inflammatory, antioxidant, hepatoprotective, and anti-mutagenic effects (Farzaei et al., 2015). Previously, Murakami et al. (1991) demonstrated intraperitoneal

injection of ellagic acid mitigates stress-induced gastric lesions and suppresses acid secretion significantly. Anti-secretory activity of ellagic acid is mediated by lowering gastric H⁺, K⁺ -ATPase activity. Likewise Bakhtaoui et al. (2014) explained that plants may act as antacids by neutralizing the acidity of the gastric fluid or by inhibiting the gastric acid secretion like cimetidine (a histamine H₂-receptor blocker) and omeprazole (a proton-pump inhibitor) effects. Plants may also act as gastric membrane protectors by preventing mucus layer erosion and/or by enhancing mucosal secretion through prostaglandin synthesis induction. They can as well counterbalance the free radical oxidant effect by scavenging them (Farzaei et al., 2015). The results obtained in this study is in line with previous data, show that aqueous extract of Pomegranate peel possess good potential as an antiulcer agent too. Additionally, no adverse effects have been reported on consuming Pomegranate and its constituents, since time immemorial, animal studies have failed to report any toxicities at doses conventionally used in the conventional system of medicine (Moghaddam et al., 2013).

5- CONCLUSION

The current study reveals a healing role of Pomegranate Peel against Aspirin -induced gastric ulcer in rats. This could be -at least partly- primarily through targeting inflammation. Secondarily Pomegranate Peel treatment attenuates ulcer damage via its healing, antisecretory and cytoprotective activities. Finally, Pomegranate Peel could promote gastric tissue repair through up regulation of angiogenesis. The present study supports the traditional claims of the use of Pomegranate Peel in treatment of ulcer.

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تأثير استخدام المستخلص المائي لقشور الرمان في شفاء قرحة المعدة في الجرذان

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الملخص: تهدف الدراسة الى معرفة تأثير المستخلص المائي لقشور الرمان في معالجة قرحة المعدة المستحدثة بواسطة عقار الأسبرين (٢٠٠ ملجم/كجم)، أستخدم في الدراسة ٣٠ جرذ من الذكور، أظهرت النتائج وجود تأثير معنوي ($p < 0.05$) للمعاملة بعقار الأسبرين حيث أدت إلى حدوث تقرحات متعددة في بطانة المعدة وكذلك حدوث ارتفاع في دليل القرحة وزيادة حجم العصير المعدي وانخفاض في قيمة الرقم الهيدروجيني (pH) للعصارة المعدية مقارنة مع بقية مجاميع التجربة الأخرى، كذلك أظهرت النتائج أن إعطاء المستخلص المائي لقشور الرمان بتركيزات ٢٠٠، ٤٠٠، ٦٠٠ ملجم/كجم أدى إلى معالجة القرحة في بطانة المعدة كما أحدث تأثيراً معنوياً ($p < 0.05$) في معايير القرحة مقارنة مع المجموعة المعالجة بالأسبرين، حيث ساهم في سرعة شفاء القرحة وتحسين المعايير السابقة الذكر واقترب من قيم المجموعة الضابطة السالبة. وكانت الجرعة المرتفعة من المستخلص المائي لقشور الرمان (٦٠٠ ملجم/كجم) الأكبر فعالية في علاج قرحة المعدة، يتبين من هذه الدراسة أن المستخلص المائي لقشور الرمان يلعب دوراً مهماً في شفاء قرحة المعدة. ومع ذلك فتوجد حاجة لإجراء دراسات أخرى تساعد على الفهم الكامل لتأثير المكونات النشيطة، ولاستكشاف الفعاليات الوقائية والعلاجية للرمان.

الكلمات المفتاحية: قرحة المعدة، المستخلص المائي لقشور الرمان، الأسبرين، الجرذان.